Anticipatory Waivers of Consent for Pediatric Biobanking

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Abstract
As pediatric biobank research grows, additional guidance will be needed about whether researchers should always obtain consent from participants when they reach the legal age of majority. Biobanks struggle with a range of practical and ethical issues related to this issue. We propose a framework for the use of "anticipatory waivers of consent," which is empirically rooted in research that shows children and adolescents are often developmentally capable of meaningful deliberation about the risks and benefits of participation in research. Accordingly, bright line legal concepts of majority or competency do not accurately capture the emerging capacity for autonomous decision-making of many pediatric research participants and unnecessarily complicate the issues about contacting participants at the age of majority to obtain consent for the continued or first use of their biospecimens that were obtained during childhood. We believe the proposed framework provides an ethically sound balance between the concern for potential exploitation of vulnerable populations, the impetus for the federal regulations governing research with children, and the need to conduct valuable research in the age of genomic medicine.

Keywords: Biobanking, pediatric biobank participants, consent at age of majority, institutional review boards, anticipatory waiver of consent

The completion of the Human Genome Project in 2003 has led to a significant increase in the number of biobanks storing human biospecimens. Research by Henderson, et al. in 2013 revealed nearly 900 biobanks operating in the United States[1] – a number that has certainly grown in the five years since their study – with the majority of biobanks engaged in genetic research.[2] Nearly 50% of these biobanks each contain more than 10,000 individual biospecimens and 44% contain at least some biospecimens collected from individuals under the age of 18.[3] Moreover, nearly half of biobanks identify their main biospecimens as "DNA".[4] This changing research landscape presents particular challenges in the pediatric context. At issue is whether researchers should obtain consent from pediatric biobank participants when they reach the legal age of consent for the first or ongoing use of their biospecimens.

Subpart D of the federal regulations governing research with humans, which describes the requirements for protections for research with children, is silent on the issue about obtaining consent from pediatric biobank participants when they reach the age of majority.[5] The only specific guidance on this issue comes from the Office for Human Research Protections (OHRP) in the Frequently Asked Questions (FAQ) section of its Web site:

> When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject's participation in the research is no longer regulated

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> by the requirements of 45 CFR part 46.408 regarding parental or guardian permission and subject assent.
>
> Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met.
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> Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects.[6]

At the heart of OHRP's recommendations is the concern that when pediatric research participants reach the age at which they can provide legal consent, they may not want to continue participating in research in which their parents enrolled them. Thus, seeking their consent when they become legal adults ostensibly respects ethical norms of respect for persons. Within the context of traditional pediatric clinical research trials, the framework suggested by OHRP mirrors established models for consent of minors that both recognize their unique vulnerabilities and seek to respect their emerging capacity to provide informed consent to participate in research.

The recent regulatory changes to the Common Rule do not contain a provision clarifying the issue about obtaining consent from pediatric biobank participants once they reach the age at which they can provide legal consent.[7] Thus, Subpart D of the Revised Common Rule remains unchanged with respect to the requirements for consent of pediatric participants and there has, as yet, been no indication that OHRP's FAQs will be revised or supplemented. These regulations and guidelines have not kept pace with current biospecimen-related research, which involves large numbers of participants of a variety of ages, potentially long-term storage of their biospecimens and associated data, and a variety of initial consent approaches. Nor do they reflect the current understanding of the developing capacity of legal minors to consent to minimal risk medical research.

We believe that the consent guidance articulated in the FAQs is overly restrictive and could have the potential to exacerbate the already marked inequities in opportunities for pediatric research participants. This, in turn could result in less innovation in treatment and prevention of diseases in both pediatric and adult contexts.[8] For example, as we become better at treating pediatric disease, research on stored biospecimens may help researchers understand and prevent long-term sequelae of pediatric disease. Additionally, the ability to use biospecimens obtained from children and adolescents after they become legal adults could provide key insights into the

prevention of serious adult conditions, such as diabetes or cardiovascular diseases.

As pediatric biobank research grows, additional guidance will be needed about whether researchers should always obtain consent from participants when they reach the legal age of majority. Biobanks struggle with a range of practical and ethical issues related to this issue.[9] For biobanks that have a single collection of biospecimens but do not follow pediatric participants longitudinally, obtaining their consent after they reach the age of majority may not be feasible. Families relocate without providing forwarding addresses and tracking of hundreds or thousands of participants could be cost-prohibitive. Additionally, linkages with paper and electronic medical records vary in the extent to which identifiable information about participants is connected to individual biospecimens and made available to researchers.[10] Brothers and colleagues suggest that researchers should consider prospectively developing plans to obtain consent from participants upon legal adulthood and that institutional review boards (IRBs) should be willing to grant "consent waivers" where attempts to recontact pediatric participants are not successful. Brothers argues these waivers should be granted even for identifiable pediatric biospecimens and associated data.[11]

We endorse the approach Brothers and colleagues proposed and in this article outline a framework for the use of "anticipatory waivers of consent." Our proposal is empirically rooted in research which has demonstrated that children and adolescents are often developmentally capable of meaningful deliberation about the risks and benefits of participation in research.[12] Accordingly, bright line legal concepts of majority or competency do not accurately capture the emerging capacity for autonomous decision-making of many pediatric research participants and unnecessarily complicate the issues about contacting participants at the age of majority to obtain consent for the continued or first use of their biospecimens that were obtained during childhood. We believe this proposal provides an ethically sound balance between the concern for potential exploitation of vulnerable populations (the impetus for Subpart D) and the need to conduct valuable research in the age of genomic medicine.

Research with Biospecimens from Pediatric Participants

Research with biospecimens from children and adolescents serves two primary purposes: to understand pediatric-specific diseases, such as many childhood cancers, which have no adult equivalent, and 2) to understand the long-term effects of the interaction between genetic and environmental exposures on adult disease and wellness.[13] For example, adult survivors of pediatric cancer experience a high rate of secondary malignancies leading to increased morbidity.[14] Longitudinal research with biospecimens might identify predictors of outcomes among adult survivors, which in turn could lead to more precise and effective administration of chemotherapy protocols in pediatric patients.

The scientific benefit of biobanking is largely owed to its aggregation of large quantities of biospecimens with an ever-increasing amount of health data that can be connected with those biospecimens. While clinical research prior to biobanking may have involved several hundred participants in a single study, as noted above, contemporary biorepositories contain considerably larger quantities of biospecimens. Indeed, 20% of biobanks now contain more than 100,000

biospecimens.[15] Because biobanking is also distinct from other areas of clinical research in that there is often no defined study or even research question at the time the biospecimens are collected, obtaining informed consent at the time biospecimens are collected can be complicated. For example, individuals may be asked to consent to future unspecified research with their biospecimens and associated data. When adults contribute their biospecimens to a biobank, they are agreeing to accept the potential risks of harm from biospecimen-related research, which include harms from disclosure to others of genetic information derived from analysis of their biospecimens.[16] Some might argue that children and adolescents are incapable of understanding these issues, as well as the fact that research with biospecimens generally will not provide a direct benefit to them. Rather, the benefit is "the possibility of accurate genetic diagnosis in the future"—arguably a group benefit.[17] Taken together, these factors seem to require that some special consideration be given to the consent process for pediatric biobank participants.

As noted earlier, Subpart D of federal research regulations, "Additional Protections for Children Involved as Subjects in Research" does not address the matter of obtaining consent from legal adults whose parents enrolled them in research when they were legal minors. Rather, it requires researchers to obtain, at the time of enrollment in research, "the assent of the children, when in the judgment of the IRB the children are capable of providing assent."[18] This determination can be based on "the ages, maturity, and psychological state of the children involved."[19] Along with the assent of the child, the IRB must determine that "adequate provisions are made for soliciting the permission of each child's parents or guardian."[20] While our proposal for an anticipatory waiver of consent in the context of pediatric biobanking acknowledges concerns about children as vulnerable populations, it also seeks to respect the emerging capacity of some children and adolescents to understand and appreciate the risks and benefits of research participation.

A Framework for Anticipatory Waivers of Consent

The complexity of obtaining consent from pediatric biobank participants when they reach the age of legal majority turns on two key issues. The first is the variety and diversity of purposes and practices of individual biobanks, which makes them poorly suited to the framework of the Common Rule.[21] The second is the role of "emerging capacity" that arises in pediatric medicine, and thus, pediatric research. Consequently, the approach to consent from pediatric biobank participants when they involve minors requires a two-tiered analysis: 1) define the nature of the research; and 2) identify the vulnerabilities implicated by the participants in a given pediatric study.

Leaving aside the legal and regulatory conceptions of consent for a moment, consent within the domain of pediatric research as it is understood from an ethical perspective is increasingly informed by an appreciation for the evolving developmental capacity of minors – particularly of adolescents – to consent to research. This evolving or emerging capacity is not adequately reflected in the legal concept of competency, which demands adherence to a bright-line rule, such as reaching the age of majority. Work done by Kipnis examining pediatric vulnerabilities, however, best captures the unique nature of vulnerability as it relates to pediatric participants in research.

Kipnis's concepts of incapacitational and juridic vulnerability are particularly salient to the issue of biobanking. Incapacitational vulnerability pertains to whether a particular research subject has the initial decisional capacity to deliberate about whether to participate in a proposed study.[22] As Kipnis notes, decisional capacity is not necessarily tied to the age of legal majority.[23] Rather, significant research indicates that minors frequently develop the ability to adequately deliberate and weigh the risks and benefits of participating in medical research well before the age of legal majority. For example, a recent analysis of the decisional capacity of children relative to clinical research indicates that decisional capacity can be present in children as young as 9.6 years, and is probable in children by the age of 12.[24] This finding is consistent with additional research demonstrating that age, family affluence, and health literacy correlate more strongly with decisional capacity than legal competency alone, with health literacy as the strongest predictor of whether an adolescent has the ability to meaningfully deliberate about participation in research.[25] Consequently, several authors have already argued for the appropriateness of using standardized competence assessments in children that do not rise and fall on the child's biological age alone.[26]

Similarly, the question of juridic vulnerability recognizes that minors are vulnerable to exploitation simply because of the "formal authority relationships that characterize many social structures."[27] One way to guard against the potential for exploitation is to include minors in the initial decision-making process to the extent they are capable of inclusion, and then to return decisional authority to them once the "formal authority relationship" has ended. However, the research noted above by Nelson, Hein, and others suggests that the investigators themselves may be in the best position to determine whether a specific vulnerability is actually undermining capacity for an individual participant.[28]

Because there is increasing evidence that many adolescents are developmentally capable of providing their consent at the initiation of minimal-risk research or when they are asked to provide their biospecimens for research, a rigid requirement to obtain consent from them when they reach the age of legal majority seems unnecessarily and overly protective to the detriment of important research. And as noted earlier, complying with such a requirement frequently will be impracticable since it would require tracking the dates when potentially thousands of biobank participants reach the age of majority and attempting to contact them, with likely inconsistent success in doing so.

A better approach that is less disruptive, but still respects the autonomy of research participants, would involve the use of anticipatory waivers of consent. As a matter of practice, this will require researchers, at the time they submit a research protocol to the IRB, to request a waiver from having to obtain consent from pediatric biobank participants when they reach the age of majority. This anticipatory waiver of consent would only be available in accordance with the existing requirements for obtaining a waiver from an IRB of the regulatory consent requirement for human subjects research: the research involves no more than minimal risk; the waiver of consent will not adversely affect the rights and welfare of the research participants; the research cannot practicably be carried out without the waiver; and when appropriate, research participants will be provided with additional pertinent information after participation.[29] We describe below three primary components of our proposed framework for an anticipatory waiver of consent.

Investigators should undertake a comprehensive initial permission-assent process.

The parental permission and child assent requirements in Subpart D of the federal regulations recognize that many children can and should be involved in the consent process for enrolling in research, and that obtaining assent is appropriate depending on the ages and maturity of the child involved. As noted above, studies have shown that many children and adolescents are capable of understanding research and should be given the opportunity to actively participate in the consent process in which parental permission for enrollment is being sought.[30] This includes potentially advising children and adolescents that enrolling in genomic research involves of a wide range of considerations, including the risk of loss of privacy, discrimination related to the findings of the research, and any conflicts of interest the researchers may have.[31] Investigators should also use this opportunity to explain to children, adolescents, and their parents that there is a possibility the researchers will not contact the participants when they become legal adults to obtain consent for continued or future research with their biospecimens.

As it relates to assessing decisional capacity, given that research demonstrates the presence of decisional capacity in children by approximately the age of 12, investigators involved in minimal-risk research may rely on their assessment of the individual's developmental level, health literacy, and age to determine whether she or he is capable of providing meaningful consent. Because there is variation in the age at which individual children and adolescents are developmentally capable of engaging in meaningful deliberation regarding research, investigators seeking from the IRB an anticipatory waiver of consent could agree to use a brief capacity assessment tool during the consent process. For example, the tool known as the University of California, San Diego Brief Assessment of Capacity to Consent, has been shown to provide an accurate picture of a potential participant's ability to consent to clinical research and takes less than five minutes to implement.[32]

Admittedly, this latitude at the research level may make some uncomfortable. However, it is important to keep in mind that "minimal risk" as specifically defined in the Common Rule does not mean risk-free. Instead, minimal risk has been defined to mean that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[33] The process of consenting to a minimal risk study is significantly less involved and less consequential than the process of, for example, enrolling in a cancer treatment study in which a participant is randomized to an experimental medication that has known, and sometimes, unknown immediate and long term effects. Accordingly, reliance on ethical concepts of emerging capacity is more appropriate than reliance on legal concepts of competency in the minimal risk research context.

IRBs should grant waivers at the time they approve research protocols.

One of the complicating factors of biobanking research is that when biospecimens are collected for future unspecified research, individuals will not know in what types of studies their biospecimens will be used. This fact alone, however, should not be dispositive of the issue of anticipatory waivers of consent. To the extent biobanks have adequate policies requiring

developmentally appropriate consent procedures, including informing participants of the nuances of biobanking research (i.e., that research is conducted over a long period of time, that a study may not be fully articulated at the time biospecimens are collected, and that unless the study poses greater than minimal risk, pediatric participants will not be contacted for consent with they become legal adults), investigators should request and be granted an anticipatory waiver of consent.

We suggest that IRBs could grant an anticipatory waiver of consent when several conditions are met: 1) the waiver is granted when children 12 years and older will be asked to provide their biospecimens for a biobank or specific study; 2) during the informed consent process children over age 12 demonstrate adequate decisional capacity to assent to research participation; 3) children and their parents are informed that the child's biospecimens might be used for future unspecified research, including research in which the participant's identity is known; 4) children and their parents are informed that when the participant reaches the age of legal majority the participant can opt out of research with their biospecimens and information about how to opt out is provided; 5) for research with their biospecimens after they reach the age of majority, researchers will use participants' last known address to contact them at least three times to obtain their consent; and 6) if researchers are unable to find participants when they research the age of majority then research with their biospecimens will go forward in accordance with an IRB-approved anticipatory waiver of consent.

The criteria above are not over-broad, as would be the case if the waiver of consent was requested for pediatric biobank participants of all ages. Nor do they impose an overly burdensome consent process for every biobank participant who reaches the legal age of majority as would be the case if IRBs followed OHRP's FAQs guidance.

Conclusions

One potential concern about the framework for anticipatory waivers of consent is the extent to which granting such waivers may undermine the public trust in biobanks or ignore individual's preferences for control over the use of their biospecimens and associated data, which could lead to parents being less likely to enroll their children in important research. The findings of one study involving adolescent patients in oncology, cardiology, and orthopedic clinics found that 50% the adolescents and 64% of their parents felt that consent at the age of legal majority for use of pediatric samples was either "important" or "very important." However, when asked whether biospecimens should still be used if attempts to obtain such consent were unsuccessful, more than half of the adolescents and their parents said yes.[34]

In another study, 60% of adult (18-34 years old) cancer survivors whose biospecimens had been obtained during their childhood thought they should be asked for consent when they became legal adults, and all of the study participants gave permission for their biospecimens to remain in the biobank.[35] These findings suggest that pediatric biobank participants are willing for their biospecimens to be used for research after they become legal adults, but that they still want to be asked for permission for such use.

Pediatric biobanking research is important to the continued advancement of medical

knowledge and technology. However, it presents challenges with respect to whether participants should be contacted for their consent when they reach the age of legal majority. In our view, the restrictive standard articulated in OHRP's FAQs fails to acknowledge the developing capacity of pediatric research participants to consent to minimal risk research and potentially imposes unduly burdensome requirements on investigators, threatening important research. Our recommendations regarding the use of anticipatory waivers of consent are consistent with previous suggestions that investigators should anticipate challenges and develop prospective plans for addressing consent issue when pediatric biobank participants become legal adults.[36] We acknowledge that our proposed framework means that IRBs are effectively being asked to be more accommodating in permitting researchers to continue or begin using biospecimens from pediatric participants without their consent when they become legal adults. As such, investigators should provide assurances to the IRB that they will 1) engage in detailed and appropriate informed consent processes at the front end of research with legal minors who are developmentally capable of engaging in the informed consent process, and 2) make efforts to contact participants when they reach the legal age of majority when contact information is available. We believe our framework is a balanced approach that promotes important research as well as the interests of biobank participants.

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